Self-enforcing feedback activation between BCL6 and pre-B cell receptor signaling defines a distinct subtype of acute lymphoblastic leukemia.

Journal: Cancer Cell

Publication Year: 2015

Authors: Huimin Geng, Christian Hurtz, Kyle B Lenz, Zhengshan Chen, Dirk Baumjohann, Sarah Thompson, Natalya A Goloviznina, Wei-Yi Chen, Jianya Huan, Dorian LaTocha, Erica Ballabio, Gang Xiao, Jae-Woong Lee, Anne Deucher, Zhongxia Qi, Eugene Park, Chuanxin Huang, Rahul Nahar, Soo-Mi Kweon, Seyedmehdi Shojaee, Lai N Chan, Jingwei Yu, Steven M Kornblau, Janetta J Bijl, B Hilda Ye, K Mark Ansel, Elisabeth Paietta, Ari Melnick, Stephen P Hunger, Peter Kurre, Jeffrey W Tyner, Mignon L Loh, Robert G Roeder, Brian J Druker, Jan A Burger, Thomas A Milne, Bill H Chang, Markus Muschen

PubMed link: 25759025

Funding Grants: Dual targeting of tyrosine kinase and BCL6 signaling for leukemia stem cell eradication

Public Summary:
Studying 830 pre-B ALL cases from four clinical trials, we found that human ALL can be divided into two fundamentally distinct subtypes based on pre-BCR function. While absent in the majority of ALL cases, tonic pre-BCR signaling was found in 112 cases (13.5%). In these cases, tonic pre-BCR signaling induced activation of BCL6, which in turn increased pre-BCR signaling output at the transcriptional level. Interestingly, inhibition of pre-BCR-related tyrosine kinases reduced constitutive BCL6 expression and selectively killed patient-derived pre-BCR(+) ALL cells. These findings identify a genetically and phenotypically distinct subset of human ALL that critically depends on tonic pre-BCR signaling. In vivo treatment studies suggested that pre-BCR tyrosine kinase inhibitors are useful for the treatment of patients with pre-BCR(+) ALL.

Scientific Abstract:
Studying 830 pre-B ALL cases from four clinical trials, we found that human ALL can be divided into two fundamentally distinct subtypes based on pre-BCR function. While absent in the majority of ALL cases, tonic pre-BCR signaling was found in 112 cases (13.5%). In these cases, tonic pre-BCR signaling induced activation of BCL6, which in turn increased pre-BCR signaling output at the transcriptional level. Interestingly, inhibition of pre-BCR-related tyrosine kinases reduced constitutive BCL6 expression and selectively killed patient-derived pre-BCR(+) ALL cells. These findings identify a genetically and phenotypically distinct subset of human ALL that critically depends on tonic pre-BCR signaling. In vivo treatment studies suggested that pre-BCR tyrosine kinase inhibitors are useful for the treatment of patients with pre-BCR(+) ALL.